Special issues for returns to participants in low-resource communities: **Lessons from the Bio*Me* project**

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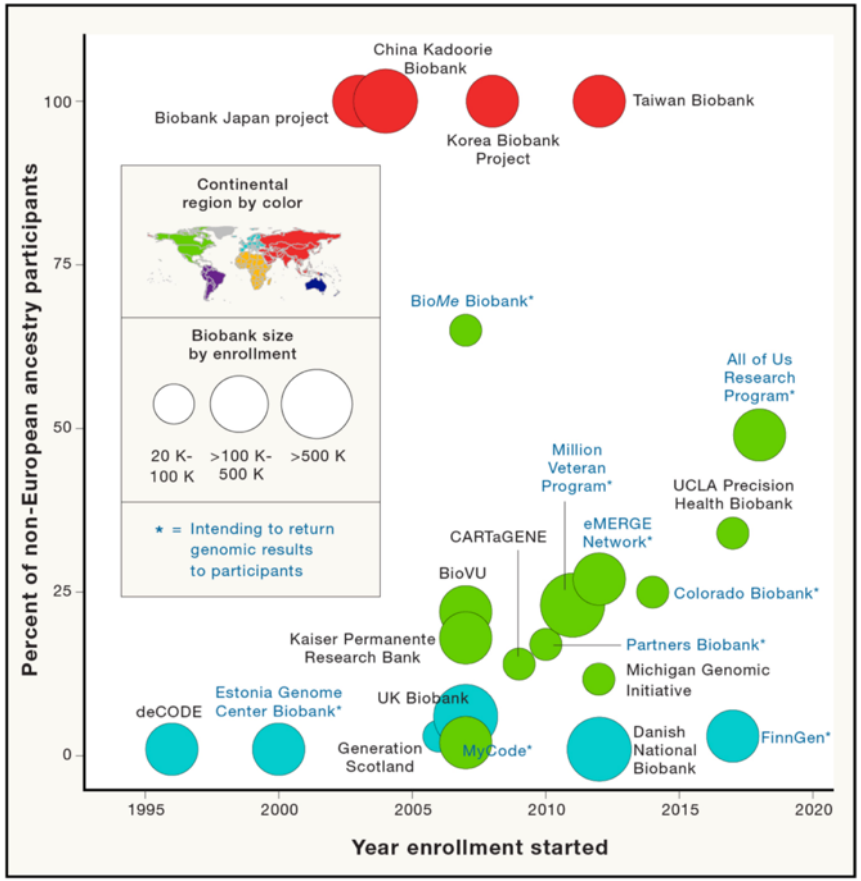
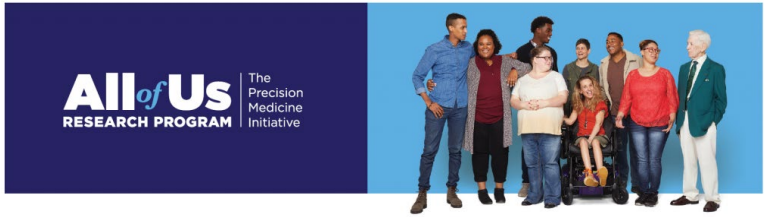
Disclosures

- 23andMe: Employee and equity holder
- Allelica: Scientific advisory board member
- Akcea: Research funding
- Genetech, Allelica, 23andMe: Personal fees
- Regeneron pharmaceuticals: Previously employed

Biobanks linking genomic and clinical data fuel genomic discovery and genomic medicine implementation





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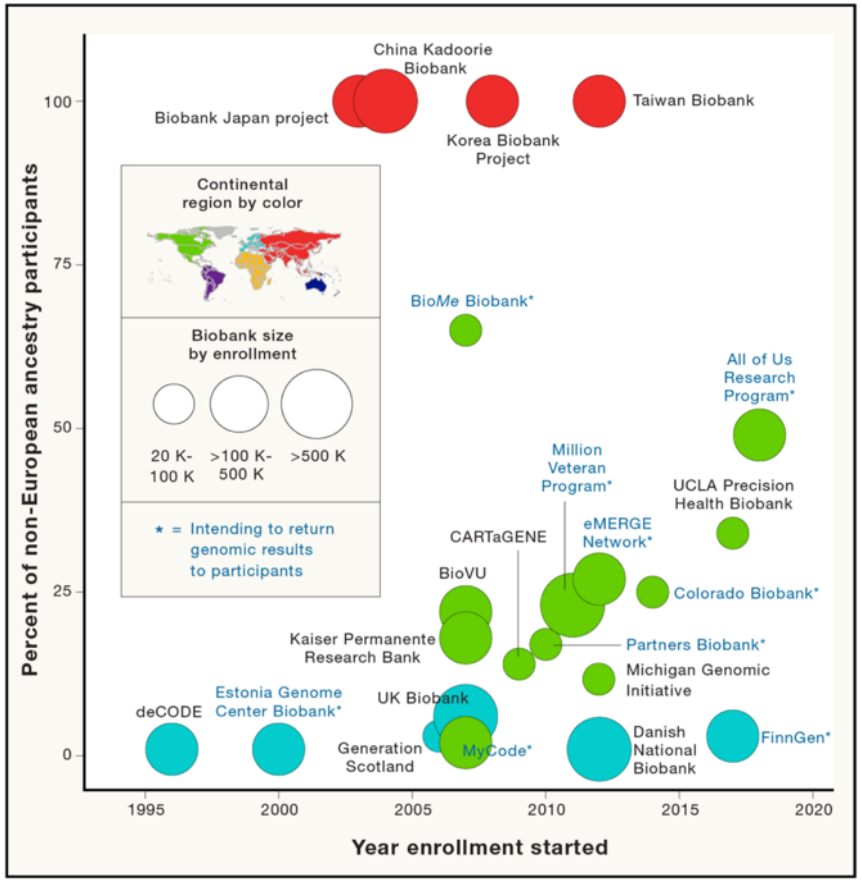
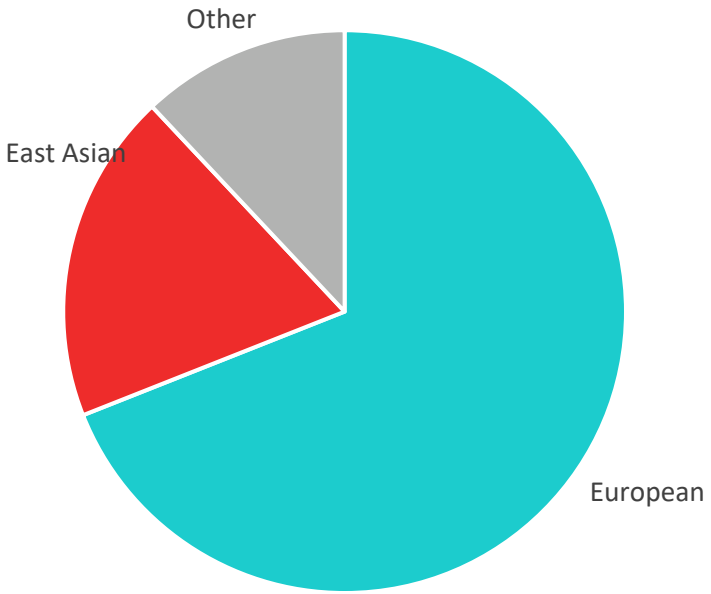
BIOBANK JAPAN

NS Abul-Husn, EE Kenny. *Cell* 2019; 177(1):58-69

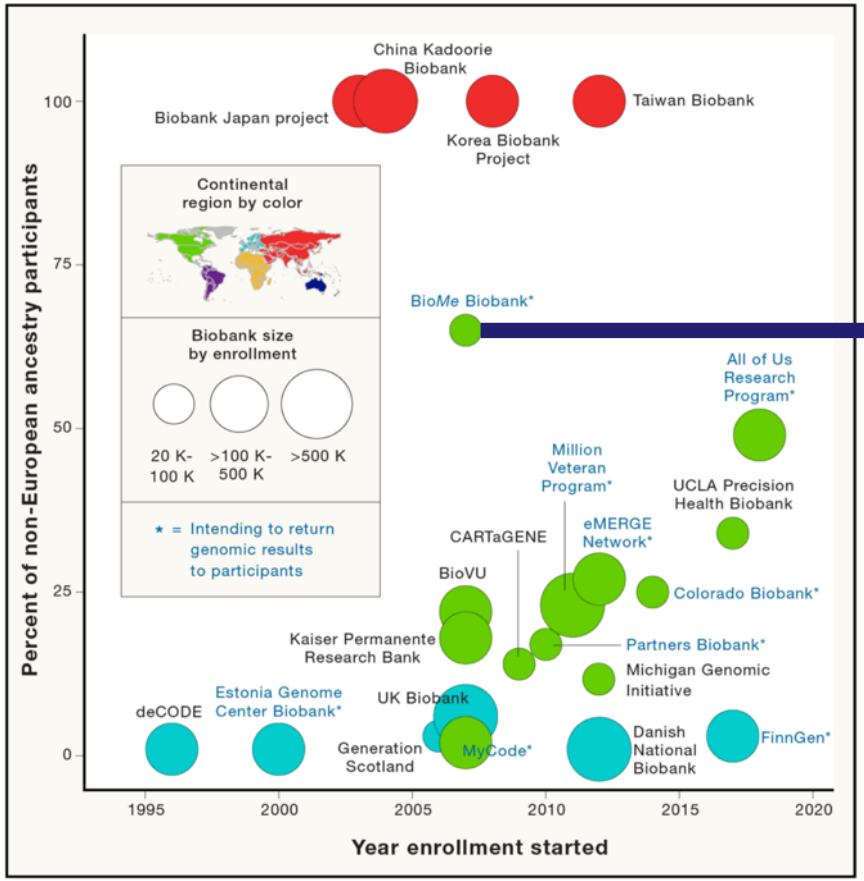
Biobank participants are not representative of global diversity

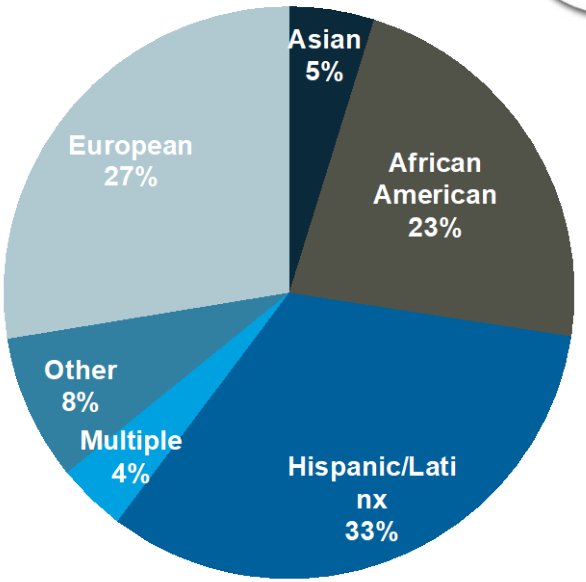




NS Abul-Husn, EE Kenny. *Cell* 2019; 177(1):58-69

Mount Sinai serves a highly diverse patient population

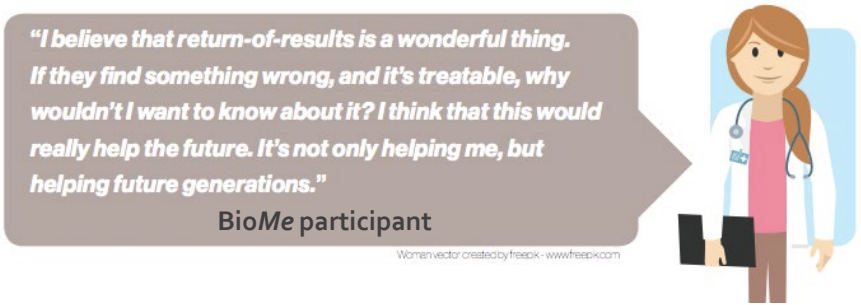




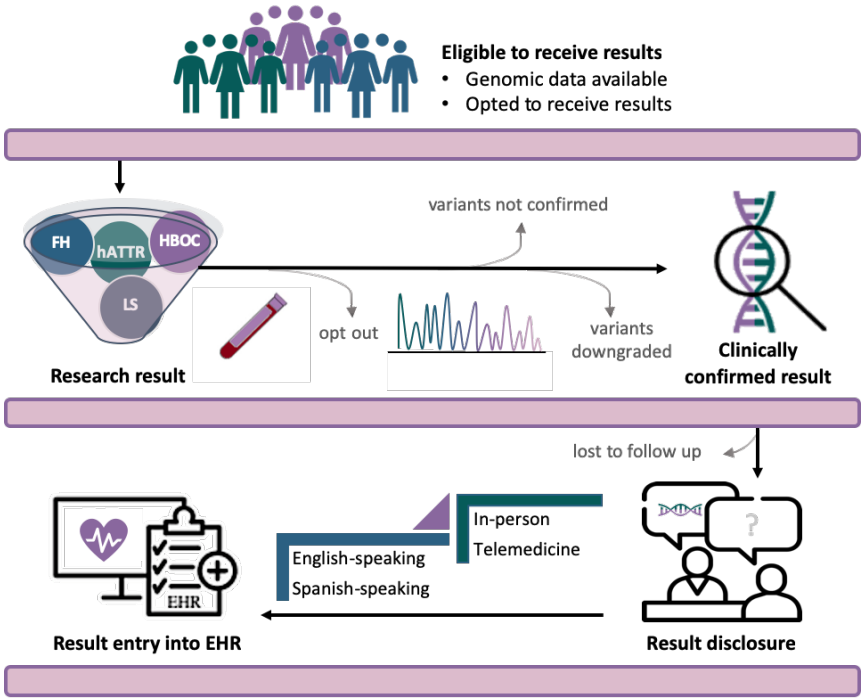
> 70,000 participants enrolled
> 55,000 with exome sequencing and genotype data
> 12,000 with genome sequencing data

Genomic screening program

Goal: Identification, confirmation, and return of medically actionable genomic results for use in clinical care



Implementing genomic screening in diverse populations requires stakeholder input



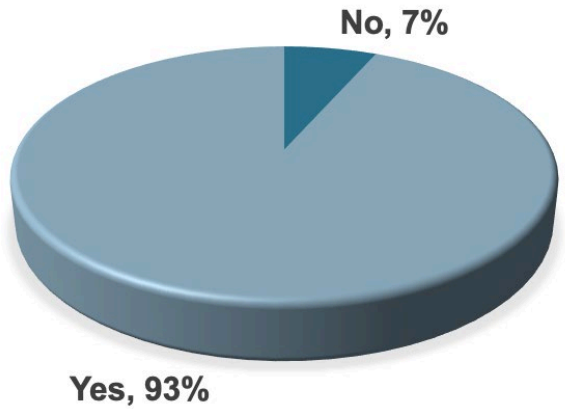
STAKEHOLDERS

- Patients, participants, communities
- Geneticist and non-geneticist domain experts
- Researchers
- Healthcare providers
- Healthcare leadership
- Payors

NS Abul-Husn *et al. Genome Med* 2021; 13(1):17

Most BioMe participants want to receive genomic results

Do you wish to receive genetic results? (N = 7461)



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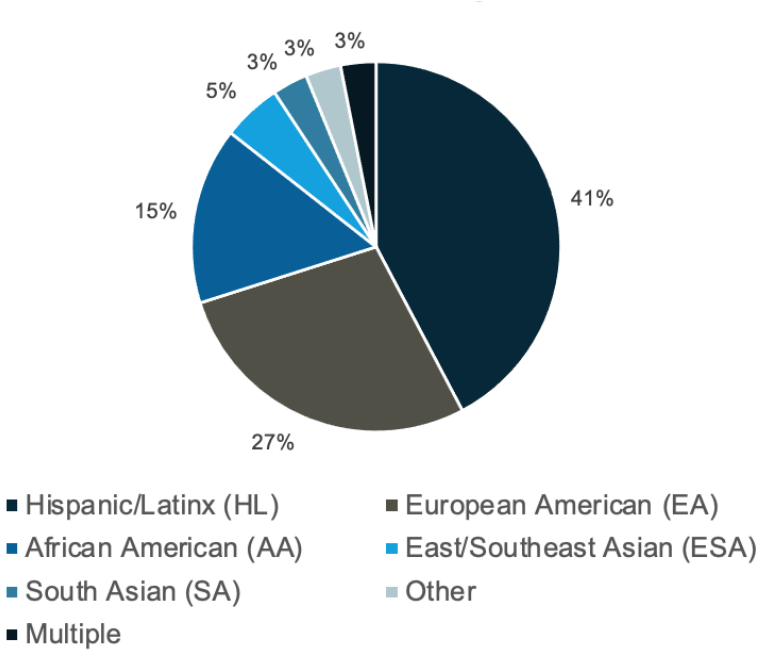
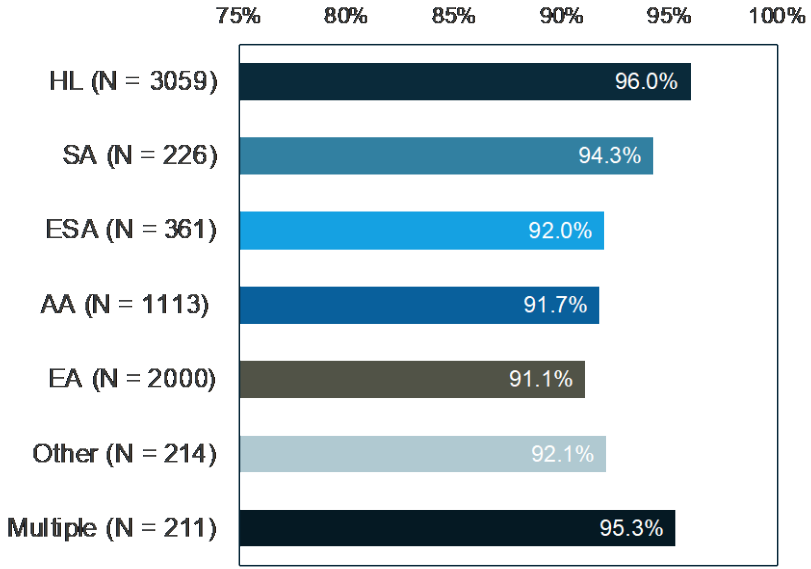
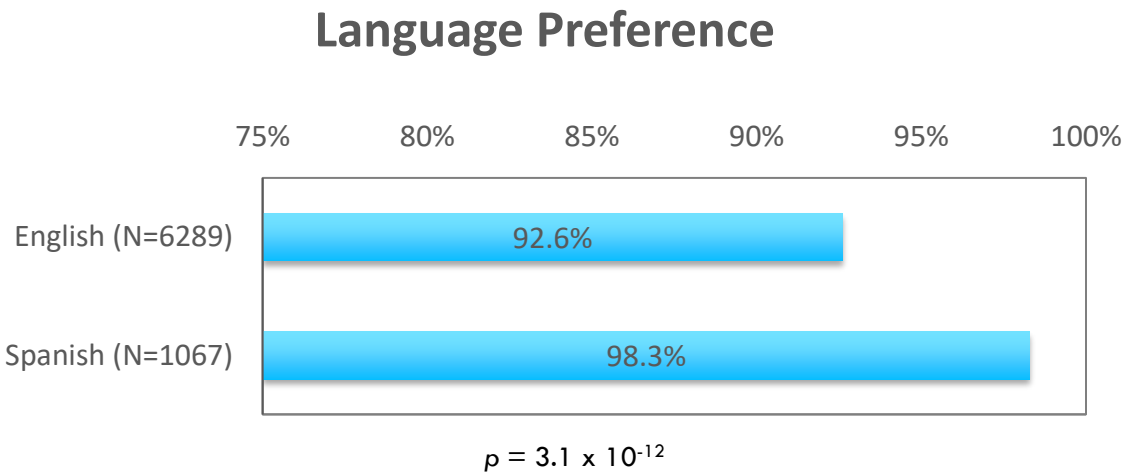


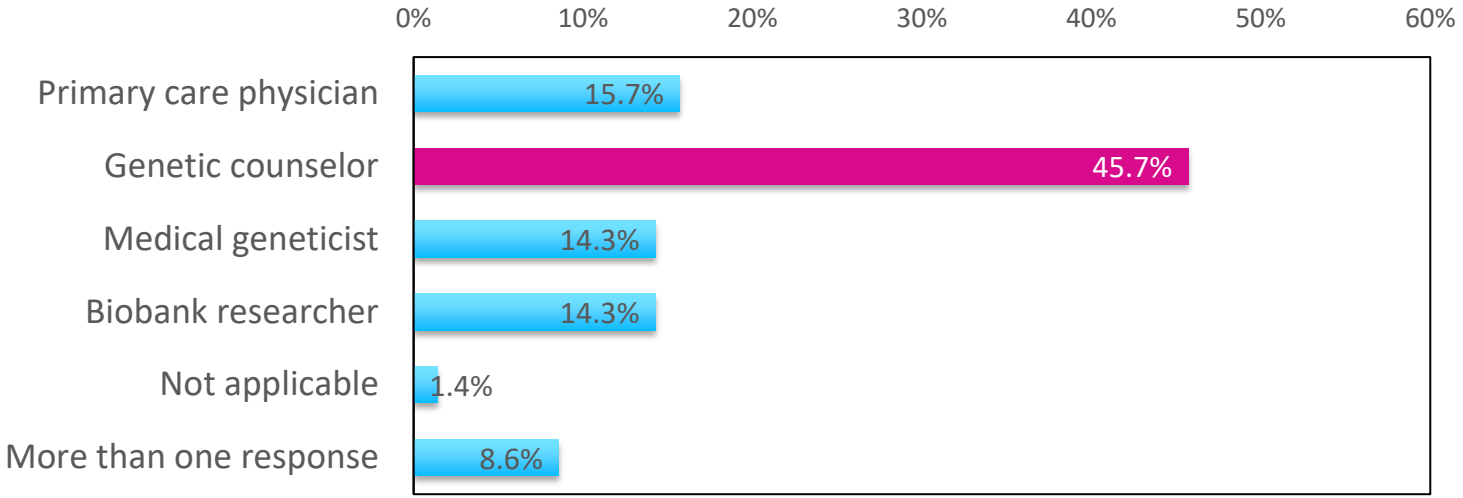


NS Abul-Husn *et al. Genome Med* 2021; 13(1):17

Spanish-speaking participants are more likely to elect to receive genomic results



How should genetic results be returned?

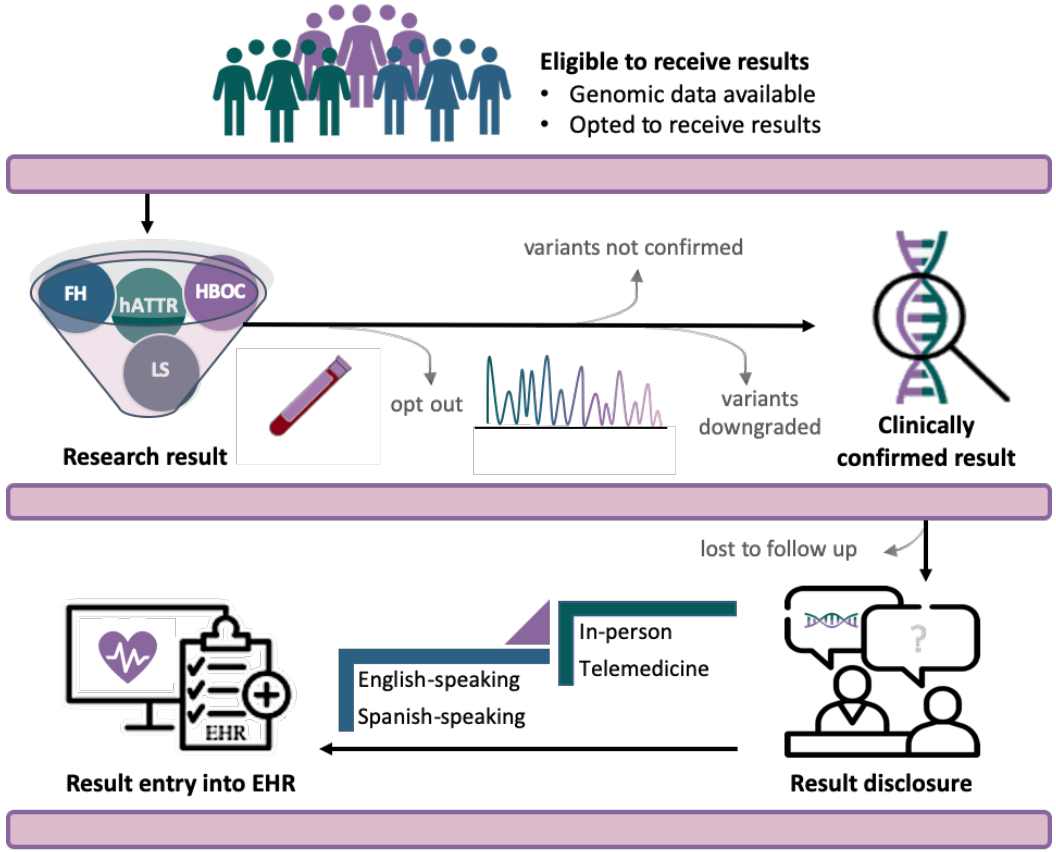


NS Abul-Husn *et al. Genome Med* 2021; 13(1):17

Genomic screening program

ACCESSIBILITY

- English- and Spanish-speaking clinical research coordinators
- Spanish translation of participant-facing materials
- Point-of-care translation services
- Flexible timing of outreach, including evenings and weekends
- In-person or telemedicine option
- RoR visits linked to existing clinical appointments



Which genes should be included?

A Proposed Approach for Implementing Genomics-Based Screening Programs for Healthy Adults

By Michael F. Murray, James P. Evans, Misha Angrist, Kee Chan,Wendy R. Uhlmann, Debra Lochner Doyle, Stephanie M. Fullerton, Theodore G. Ganiats, Jill Hagenkord, Sara Imhof, Sun Hee Rim, Leonard Ortmann, Nazneen Aziz, W. David Dotson, Ellen Matloff, Kristen Young, Kimberly Kaphingst, Angela Bradbury, Joan Scott, Catharine Wang, Ann Zauber, Marissa Levine, Bruce Korf, Debra G. Leonard, Catherine Wicklund, George Isham, and Muin J. Khoury

Box 2 | Suggested Tier System for Genomics-Based Screening Programs

TIER 1

- Lynch syndrome-associated genes *(MLH1, MSH2, MSH6, PMS2, EPCAM)*
- Hereditary Breast and Ovarian Cancer (HBOC)-associated genes *(BRCA1, BRCA2)*
- Familial hypercholesterolemia (FH)-associated genes *(LDLR, APOB, PCSK9)*

TIER 2

- Genes with unknown or low penetrance
- Genes with a less well-established knowledge base
- Efficacious interventions available
- Follow-up confirmatory tests available
- Examples including but not limited to *PALB2,* hereditary hemochromatosis, malignant hyperthermia, hypertrophic cardiomyopathy, long QT syndrome, pharmacogenomic variants

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https://www.cdc.gov/genomics/implementation/toolkit/tier1.htm

Genomic screening in diverse populations

	Risk Condition	Gene(s)
CDC Tier 1 Genomic Conditions	Hereditary Breast and Ovarian Cancer	*BRCA1* *BRCA2*
	Lynch Syndrome	*MLH1* *MSH2* *MSH6* *PMS2*
	Familial Hypercholesterolemia	*LDLR* *APOB* *PCSK9*
Tier 2	**Hereditary TTR Amyloidosis (hATTR)**	***TTR***

GenomicsFirst Committee

The GenomicsFirst Committee is a team of internal experts in genomic medicine at Mount Sinai. This committee was established to guide efforts in the development and use of genomic screening in clinical care across the Mount Sinai Health System.

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NS Abul-Husn *et al. Genome Med* 2021; 13(1):17

Why hATTR?

Penetrance	The most common *TTR* variant, V142I, is associated with ~60% increased risk of heart failure
Diagnosis	Only 11% of individuals harboring *TTR* V142I with heart failure have a diagnosis of hATTR
Actionability	New treatment options delay progression of (but do not reverse) hATTR-related amyloidosis

NS Abul-Husn *et al. Genome Med* 2021; 13(1):17

Why hATTR?

Prevalence	The most common *TTR* pathogenic variant, TTR V142I, is present in 4% of African American and 1% of Hispanic/Latino individuals
Penetrance	The most common *TTR* variant, V142I, is associated with ~60% increased risk of heart failure
Diagnosis	Only 11% of individuals harboring *TTR* V142I with heart failure have a diagnosis of hATTR
Actionability	New treatment options delay progression of (but do not reverse) hATTR-related amyloidosis

NS Abul-Husn *et al. Genome Med* 2021; 13(1):17

ACMG STATEMENT

ACMG SF v3.1 list for reporting of secondary findings in clinical exome and genome sequencing: A policy statement of the American College of Medical Genetics and Genomics (ACMG)

TTR added to ACMG SF v3.1 list in July 2022

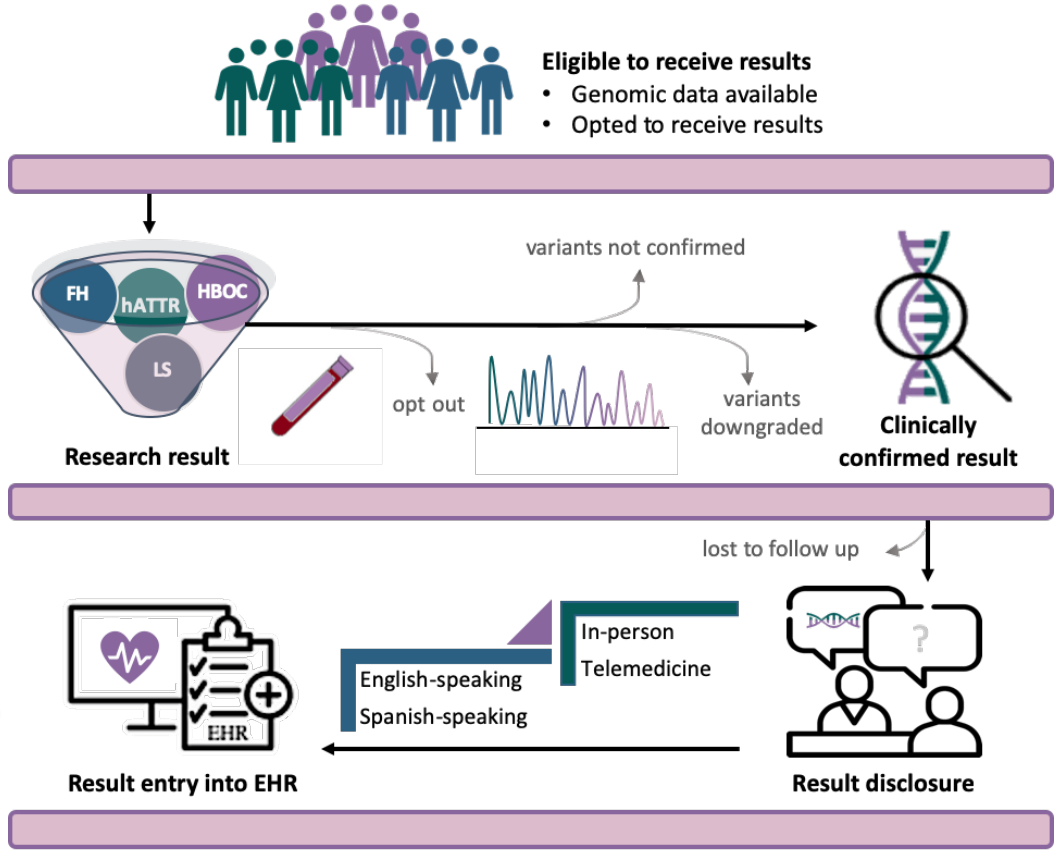
Table 2 New gene/phenotype pairs for SF v3.1 list

Gene/Phenotype	Additional Comments
Genes related to cardiovascular phenotypes	
BAG3/cardiomyopathy	Similar prevalence/penetrance rates to other DCM genes already on ACMG SF list; also associated with skeletal myopathy
DES/cardiomyopathy	Similar prevalence/penetrance rates to other DCM genes already on ACMG SF list; also associated with skeletal myopathy
RBM20/cardiomyopathy	Clear screening guidelines endorsed by ACMG; missense in 5 codons are known P/LP; few examples of LoF that are P/LP
TNNC1/cardiomyopathy	Similar prevalence/penetrance rates to other DCM genes already on ACMG SF list
Genes related to miscellaneous phenotypes	
TTR/hereditary TTR (transthyretin) amyloidosis	Nonspecific features leading to potential morbidity (heart failure); availability of treatment that may be more efficacious earlier in disease progression; high prevalence in individuals with West African ancestry

ACMG, American College of Medical Genetics and Genomics; *DCM*, dilated cardiomyopathy; *LoF*, loss of functions; *LP*, likely pathogenic; *P*, pathogenic.

DT Miller, K Lee, NS Abul-Husn, *et al.* ***Genet Med.*** 2022; 24(7):1407-1414

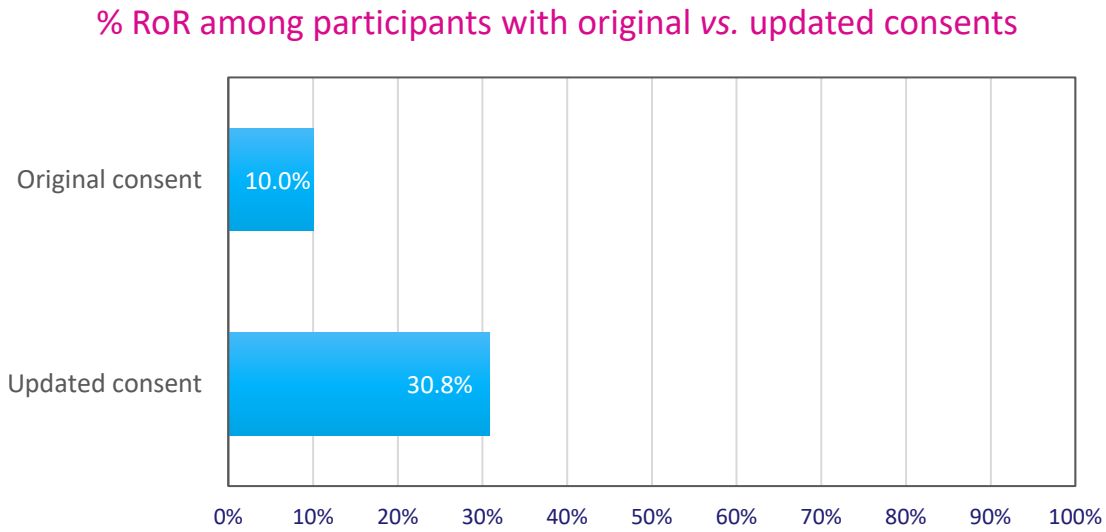
Implementation



Evaluation

Consenting to receive results at time of enrollment leads to increased rate of result return

- Bio*Me* protocol was amended in October 2018 to include the option for RoR
- Participants enrolled ***prior*** to this amendment need to update their consent in order to be eligible for RoR

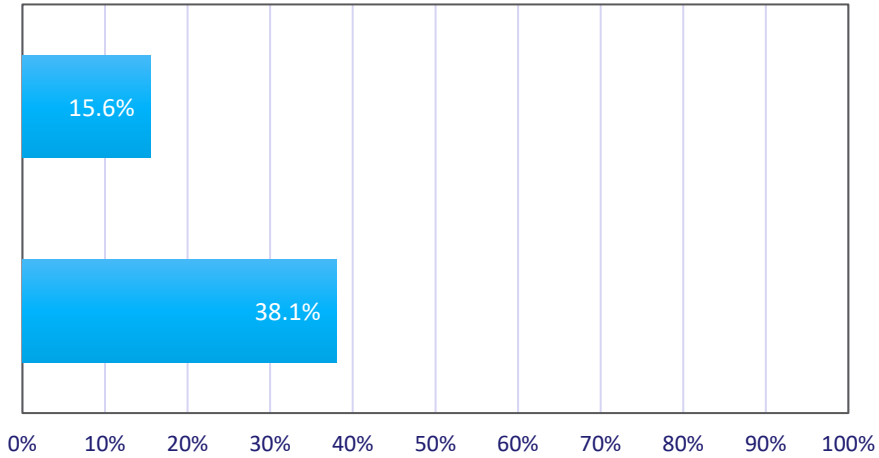


ER Soper *in preparation*

Consenting to receive results at time of enrollment leads to increased rate of result return

- Rates of recontact
  - Original consent: 64%
  - Updated consent: 81%

% RoR among **recontacted** participants with original *vs.* updated consents



ER Soper *in preparation*

What do we find when we screen for *TTR*?

32 participants receiving *TTR* V142I result

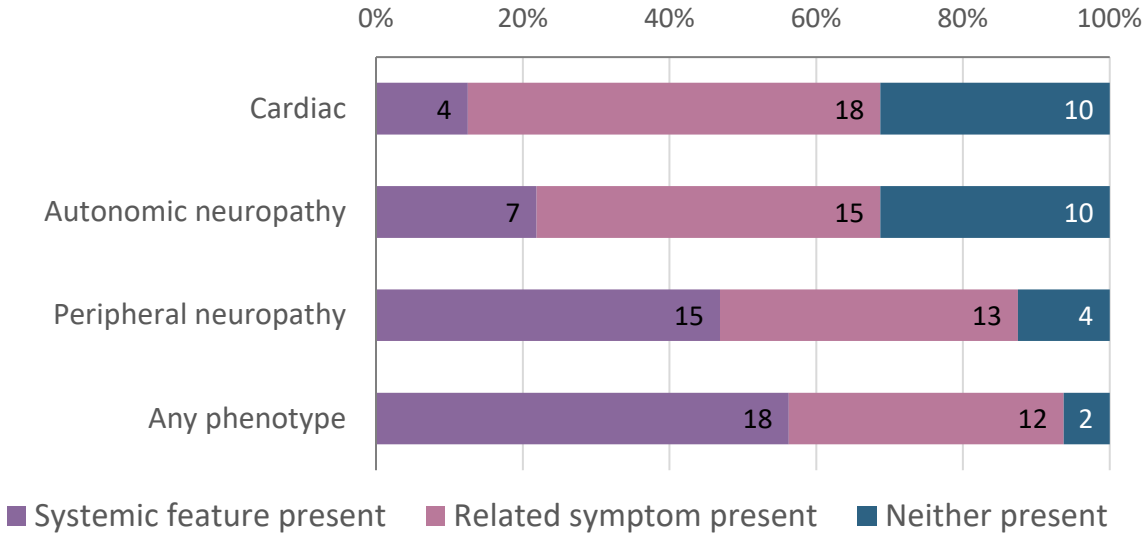
0 PRIOR GENETIC TESTING/DIAGNOSIS

4 HEART FAILURE

1 CARDIAC AUTONOMIC DYSFUNCTION
4 INCONTINENCE
3 SEXUAL DYSFUNCTION/IMPOTENCE

10 CARPAL TUNNEL SYNDROME
10 SPINAL STENOSIS

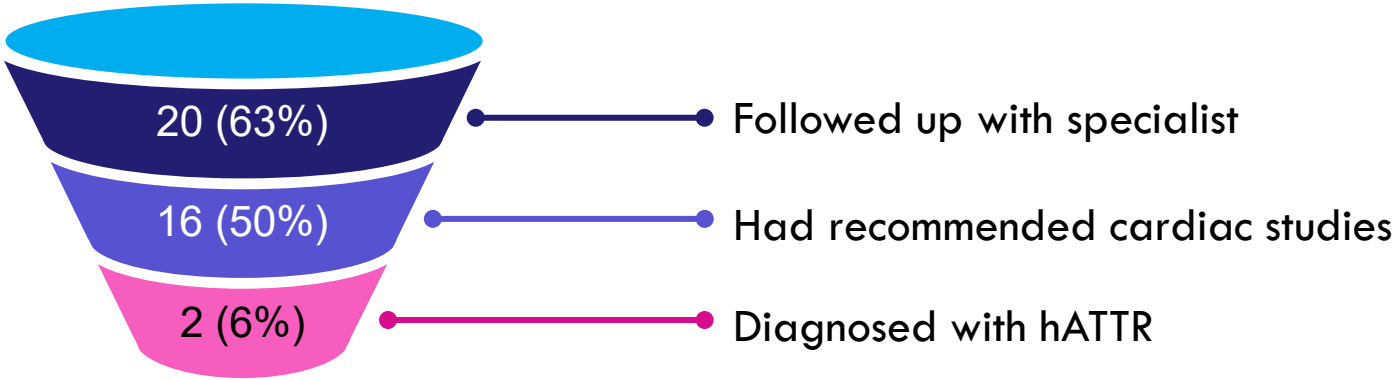
Over half had hATTR-related systemic features at time of result disclosure



ER Soper *et al. J Pers Med* 2021; 11(1):49

What do people do after receiving results?

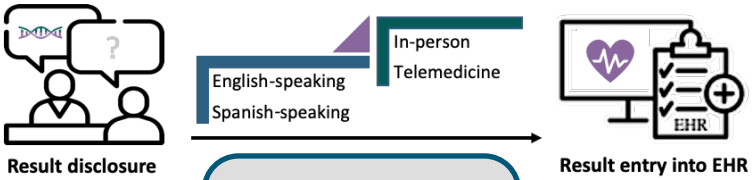
32 participants receiving *TTR* V142I result



8 month follow-up

ER Soper *et al. J Pers Med* 2021; 11(1):49

Evaluating outcomes from genomic screening for hATTR



- Prior diagnosis
- Prior genetic testing
- Relevant personal and/or family history

- Uptake of recommendations
- New diagnosis
- Change in management

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NS Abul-Husn *et al. Genome Med* 2021; 13(1):17
ER Soper *et al. J Pers Med* 2021; 11(1):49

Promoting health equity through genomics

1. Increase diversity in genomics research to generate knowledge that benefits all populations
2. Design and implement pilot genomic screening programs tailored to diverse populations
3. Collect and analyze outcomes data from genomic screening programs to inform further research

Perspective | Published: 28 October 2020

Strategic vision for improving human health at The Forefront of Genomics

ED Green *et al*. *Nature* 2020

Bold predictions for human genomics by 2030	Individuals from ancestrally diverse backgrounds will benefit equitably from advances in human genomics.

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Randi Zinberg, MS, CGC

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BioMe Biobank
Your history is our future.

THANK YOU
to the millions of biobank research participants who make this work possible

Institute for Genomic Health

Icahn School of Medicine at Mount Sinai

NIH National Human Genome Research Institute

NIH National Heart, Lung, and Blood Institute

Thank You

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